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Is there any link between mortality from COVID-19 infection and QRS duration in healthy people?

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Abstract

Aim: Cardiac involvement in COVID-19 infection is associated with in-hospital mortality and morbidity. This study aimed to evaluate the effects of COVID-19 infection on the heart in patients without any known chronic disease using electrocardiographic (ECG) parameters.

Material and Methods: The study included a total of 201 consecutive patients, including 150 survivors and 51 non-survivors, who were otherwise healthy and did not take any medication.

Results: The QRS duration, heart rate, troponin I, C-reactive protein (CRP), D-dimer and procalcitonin values were higher in the non-survivor group ($p<0.05$). Cox regression analysis showed that QRS duration [HR 1.038 (1.006–1.071), p=0.023], troponin I [HR 1.255 (1.045–1.506), p=0.035], CRP [HR 1.004 (1.002–1.007), p=0.001], and D-dimer [HR 1.000 (1.000–1.003), p=0.014] values were associated with a high mortality rate due to COVID-19. ROC analyses indicated that the cut-off value of QRS duration predictive of COVID-19 mortality was >85 ms [AUC: 0.615, 95% CI (0.519–0.711), p=0.014]. Kaplan-Meier survival analysis showed that a patient with QRS>85 ms had a higher in-hospital mortality rate at day 30.

Discussion: Patients with COVID-19 infection who were otherwise healthy and did not take any medication had a wide QRS duration and an increased risk of mortality during the first admission to the hospital. ECG may be useful for estimating COVID-19 mortality because of its quick and easy results.

Keywords

COVID-19, Heart, Electrocardiography, Mortality, Inflammation

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Introduction

SARS-CoV-2 (COVID-19) remains an epidemic disease that emerged at the end of 2019 and is transmitted through the respiratory system, leading to acute respiratory distress syndrome, multiorgan failure and high mortality [1]. It is very fatal, especially in [5,6]. Electrocardiographic changes, such as ST-T segment, QRS voltage, QT and QTc interval, prolongation of AV conduction, and atrial or ventricular arrhythmias may be observed, indirectly reflecting the effects of COVID-19 on the myocardium [6,7]. Previous studies on cardiac involvement in COVID-19 infection included complex groups with chronic comorbid diseases. However, the presence of comorbid diseases, such as coronary artery disease (CAD), diabetes mellitus (DM), hypertension (HT), and chronic obstructive pulmonary disease (COPD), adversely affect the heart, leading to various ECG changes, and COVID-19 is more fatal in these patients [4-6].

Therefore, unlike previous studies, we aimed to investigate electrocardiographic parameters in patients who did not have a known chronic disease or did not use any medication and who were hospitalized for the first time due to COVID-19.

Material and Methods

This retrospective study included 3023 consecutive patients who presented to our hospital with a complaint of cough, fever and shortness of breath and were hospitalized for the first time with a diagnosis of COVID-19 infection between June 2020 and February 2021. Patients under the age of 18 years and over 65 years who were pregnant or puerperal and had a chronic disease, patiens with right or left bundle branch block (LBBB) on their ECG were excluded from the study. Among the remaining 837 patients, 201 patients with an admission ECG who did not use any medication due to COVID-19 or any other disease were included (Figure 1). Following the World Health Organization (WHO) guidelines, nasopharyngeal swab specimens were collected from all patients, and COVID-19 was detected using a reversetranscription-polymerase chain reaction (RT-PCR) assay test. All patients underwent thoracic computed tomography (TCT) scans to confirm the diagnosis. Demographic characteristics, laboratory parameters and clinical features on the admission of all patients were obtained from their medical records at our hospital. The highest level of troponin I was 0.02 ng/mL, C-reactive protein (CRP) was 10 mg/dL, procalcitonin was 0.05 ng/mL, ferritin was 150 ng/mL, and D-dimer was 250 ng/mL. All patients received favipiravir treatment for COVID-19 during their hospitalization and appropriate antibiotic therapy if they had concomitant pneumonia.

The primary endpoint of the study was death due to COVID-19, which was acute respiratory distress syndrome. The patients were divided into 2 groups: those who recovered after COVID-19 infection (survivor group) and those who died from respiratory failure due to COVID-19 (nonsurvivor group).

Electrocardiography

The ECGs of patients diagnosed with COVID-19 on the first day of admission to the hospital were obtained. All patients received a 12-lead ECG in the supine position (GE Marquette Mac 1200). Each ECG was taken at a paper speed of 25 mm/s, a gain of 10 mV, and a paper format of 3x4. ECGs were independently interpreted by two cardiologists. The QRS duration was defined as the time interval from the onset to the end of the QRS complex, and the QT interval was measured from the onset of the QRS complex to the end of the T-wave. The corrected QT (QTc) interval was measured using Bazett's formula (cQT = QT ms / RRs) [8].

Follow-up

All patients were followed up from the first day of admission to the hospital until the day of discharge. The primary endpoint of the study was death due to COVID-19 infection.

Statistical analysis

Statistical analysis was performed using SPSS 20.0 (IBM Corporation, Armonk, NY, USA). Continuous variables were represented by mean ± standard deviation (SD) or median (minimum-maximum), categorical variables were expressed with n (number) and percentages (%). Normality assumptions were checked by the Shapiro-Wilk and Kolmogorov-Smirnov tests by the number of cases in the groups. Baseline characteristics of the COVID-19 patients were compared using the Student's t-test for continuous variables, which were normally distributed and the Pearson's x2 test was used for categorical variables. Cox regression analyses were performed for the association between QRS duration, inflammatory parameters and mortality of COVID-19. Hazard ratios and their confidence intervals were reported for univariable and multivariable models. The Kaplan-Meier survival analysis was performed to estimate the cumulative 30-day risk of death when patients were stratified by QRS duration. The receiver operating characteristics curve analysis (ROC) was used to determine the optimal cut-off of the QRS duration in a prediction model for mortality of COVID-19. For all statistics, a two-tailed p-value below 0.05 was considered significant.

Ethical Approval

Ethics Committee approval for the study was obtained.

Results

A total of 201 consecutive patients diagnosed with COVID-19 were included in the study. The mean age of the patients was 42.8 ± 15.1 years in the survivor group (n=150) vs. 52.3 ± 10.3 years in the nonsurvivor group (n=51). There was no difference between the two groups in terms of sex, body mass index, smoking or duration of hospitalization. Oxygen saturation was lower in the nonsurvivor group (p<0.000) (Table 1).

In the non-survivor group, bilateral thoracic involvement (p=0.011), mechanical ventilation (p<0.000), days in the intensive care unit (p=0.005), serum glucose (p<0.000), creatinine (p=0.003), CRP (p<0.000), procalcitonin (p<0.000), D-dimer (p<0.000), ferritin (p=0.005), troponin I (p=0.026), white blood cell count (p<0.000) and neutrophil/lymphocyte ratio (p=0.001) were higher than in the survivor group. The heart rate (p<0.000), QRS duration (p=0.010), and QT interval (p=0.002) were higher in the non-survivor group (Figure 1). The results are shown in Table 1.

Univariable and multivariable Cox regression analyses were performed to define the risk (hazard ratio) of mortality associated with COVID-19. In multivariable Cox regression analysis, QRS duration [HR 1.038 (1.006–1. 071), p=0.023], troponin I elevation [HR 1.255 (1.045–1.506), p=0.035], CRP elevation [HR 1.004 (1.002–1.007), p=0.001], and D-dimer

elevation [HR 1.000 (1.000–1.003), p=0.014] were associated with COVID-19 mortality (Table 2).

In the ROC analyses, the cutoff QRS duration to predict COVID-19 mortality was >85ms [AUC: 0.615, 95% CI (0.519–0.711), p = 0.014], with a sensitivity of 60% and a specificity of 62% (Figure 2). The Kaplan-Meier survival analysis showed that a patient with a QRS>85 ms had a higher in-hospital mortality rate at 30 days (Table 3, Figure 3).

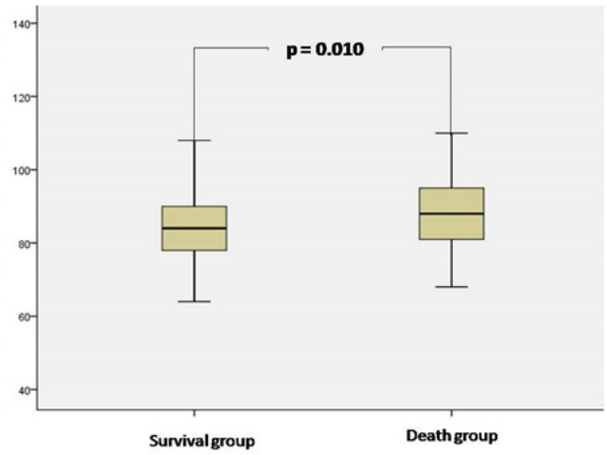

Figure 1. Comparison of QRS duration between surviving and dead patients with COVID-19.

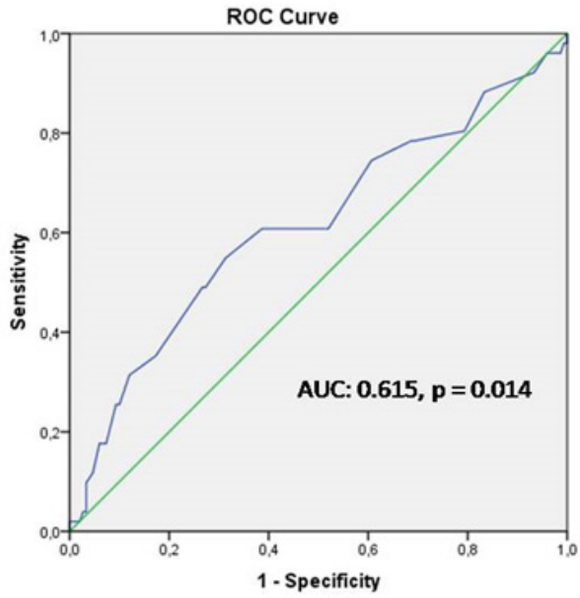

Figure 2. The demonstration of the ROC curve for the predictive value of QRS>85 ms with 60 % sensitivity and 62 % specificity [AUC: 0.615, 95 % (0.519 – 0.711), p = 0.014].

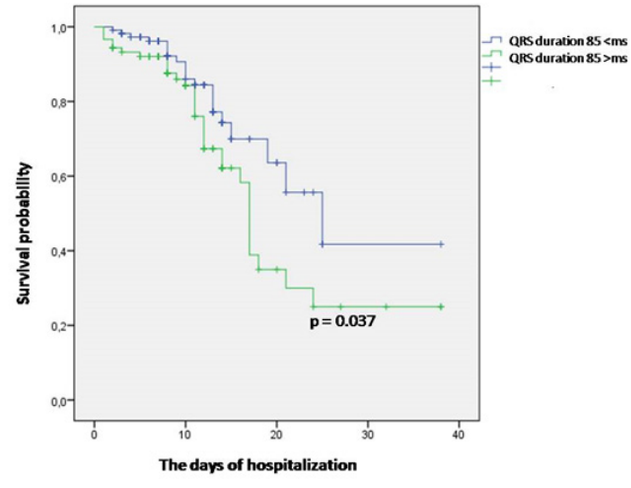

Figure 3. Kaplan-Meier Survival Analysis Stratified by QRS duration group.

Table 1. Demographic and clinical features of COVID -19 patients.

Variables	Survival (n=150)	Death (n=51)	p-value
Age, years	42.8±15.1	52.3±10.3	0.000
Sex (Male),%	90 (%60)	34 (66.7)	0.614
SO2, %	96.3±2.9	84.6±8.8	0.000
CT, bilateral involvement	37 (24.7)	22 (43.1)	0.011
MV, day	0.0±0.0	7.1±6.8	0.000
MV, %	2 (1.4)	41 (80.4)	0.000
Intensive care hospitalization day	1.4±2.3	9.1±8.2	0.005
Glucose, mg/dL	105.4±30.3	136.0±49.1	0.000
Creatine, mg/dL	0.8±0.2	0.9±0.3	0.003
GFR, mL/min/1.73m2	107.6±15.7	89.6±26.4	0.000
C-reactive protein (mg/L)	38.8±65.7	142.2±153.1	0.000
Procalcitonin, ng/mL	0.05±0.01	0.24±0.17	0.000
D-dimer, ng/mL	220.2±317.9	2090.3±4399.9	0.000
Ferritin, ng/mL	325.2±462.2	828.3±690.6	0.005
Troponin I (ng/mL)	0.007±0.043	0.301±1.609	0.026
WBC, x103 u/L	7.4±3.7	11.8±7.4	0.000
Neutrophil/lymphocyte ratio	9.8±8.2	16.9±20.8	0.001
Heart rate (bpm)	84.0±18.9	96.1±24.6	0.000
QRS duration, ms	84.0±9.2	90.2±12.1	0.010
QRS > 85 ms	58 (38.7)	31 (60.8)	0.005
QT interval, ms	371.9±37.7	350.2±38.7	0.002

Abbreviations: BMI: Body Mass Index, CT: Computed tomography, SO2: Oxygen saturation, Estimated Glomerular Filtration Rate, MV: Mechanical Ventilation, White blood cell.

Table 2. The association between inflammatory parameters, heart rate, QRS duration and death with Cox regression analysis

Variables	Univariable analysis		Multivariable analysis	
	HR (95.0 % CI)	p-value	HR (95.0 % CI)	p-value
Age, years	1.014 (0.995-1.034)	0.156		
Heart rate, bpm	1.007 (0.995-1.018)	0.258		
QRS duration, ms	1.030 (1.002-1.058)	0.038	1.038 (1.006-1.071)	0.023
Troponin I (ng/mL)	1.256 (1.057-1.492)	0.017	1.255 (1.045-1.506)	0.035
CRP, mg/dL	1.003 (1.002-1.005)	0.000	1.004 (1.002-1.007)	0.001
D-dimer, ng/mL	1.000 (1.000-1.002)	0.037	1.000 (1.000-1.003)	0.014
Ferritin, ng/mL	1.000 (1.000-1.001)	0.427		

Abbreviations: bpm: Beats per minute, CRP: C-reactive protein.

Table 3. Relationship between in-hospital 30-day mortality and QRS duration.

The mean and median time for death and QRS duration				
	Mean		Median	
	Estimate	95 % CI (Lower-Upper)	Estimate	95 % CI (Lower-Upper)
QRS ≤ 85 ms	25.732	20.586-30.320	25.000	16.832-33.168
QRS > 85	19.879	16.075-17.000	17.000	16.127-17.873
Overall	22.557	19.479-25.636	19.000	16.160-21.840

Discussion

We found that the prolongation of QRS duration and increased inflammatory biomarkers were associated with mortality due to COVID-19 infection in healthy individuals. In addition, patients with a QRS>85 ms were found to have a high mortality rate due to COVID-19 infection.

Inflammatory parameters and high troponin levels are known to be associated with COVID-19 infection mortality, but the relationship between the prolongation of QRS and mortality has not been demonstrated in healthy individuals. Our study is the first to find that prolonged QRS duration was equally associated with increased mortality compared to other inflammatory biomarkers. The studies conducted thus far included many patients with various chronic diseases who thus received various medications, and numerous ECG parameters were found to be associated with COVID-19 mortality in these studies. Some studies have shown that both QRS and QT durations are associated with poor prognosis [4,9,10,11]. However, these patients were taking chloroquine and various other drugs. In contrast, patients with any chronic disease or taking any medication were excluded from our study. ECGs were taken before the initiation of treatment for COVID-19. Therefore, the bias was reduced in the ECG parameters included in the study.

Similar to our study, Lanza et al. evaluated the ECGs of COVID-19 patients admitted to the emergency department [9]. After a one-month follow-up, they found that QRS duration ≥110ms, LBBB, and the presence of any ECG abnormality were independent risk factors associated with mortality [9]. Similarly, a study by De Vita et al. in patients with and without COVID-19 who had acute infectious respiratory disease found that a wide QRS duration and LBBB were seriously associated with COVID-19-related mortality [10]. Poterucha et al. found that a wide QRS duration and a high troponin level were associated with mortality, along with other ECG changes [11]. These studies included patients with multiple chronic diseases, especially CAD; therefore, these results might have been unfavorable for those with heart disease. However, our patient population was homogeneous and treatment-naive when compared with other studies, and they did not use any drugs that could prolong the QRS duration.

The exact reason why patients with a wide QRS duration who were admitted to intensive care units due to COVID-19 had a higher mortality rate is unknown. There may be several explanations for the prolongation of QRS duration in patients with severe COVID-19 infection. First, COVID-19 may cause myocarditis by damaging the myocardium [12-14]. Inflammation of the cardiac muscles due to myocarditis may lead to cellular edema, thickened myocardial tissue, prolonged conduction through the myocardium and thus prolongation of the QRS duration. Another reason is that COVID-19 may lead to a systemic immune reaction [12,13]. In addition, COVID-19 may directly or indirectly affect the cardiac conduction system through immune mediators as a result of the activation of systemic inflammatory pathways, and thus, a wide QRS duration may cause intra- or interventricular conduction delay [3,7]. In our study, although the QRS durations were below the normal limits in the non-survivor group, the high mortality rate and higher troponin values in this group suggest that these patients might have presented with myocarditis [3,15,16]. Cardiac involvement of COVID-19 may be predicted indirectly by elevated troponin, BNP and electrocardiographic or echocardiographic parameters [14-16]. The mortality rate due to COVID-19 with myocardial damage reached almost 40% in one series [17]. The risk of mortality associated with acute cardiac injury was found to be more significant than that associated with age, DM, chronic pulmonary disease, and prior heart disease [18]. Although there is no definitive evidence showing the presence of COVID-19 in myocardial tissue in autopsy studies for myocarditis, RT-PCR analyses of heart tissue have detected the viral genome in 35% (n=7/20) of patients [14,19]. At the same time, cardiac hypertrophy and decreased ACE 2 levels were observed in these patients [19,20]. In our study, we could not make a definitive diagnosis of myocarditis, since no cardiac biopsy or cardiac MRI was performed in any patient. However, the elevation of troponin I along with other inflammatory biomarkers increases the possibility of myocarditis. Thus, severe myocarditis and associated QRS prolongation might have increased the mortality in patients.

Limitation

The most important limitation of our study was that it was a single-center, retrospective study, and the number of patients was limited. On the other hand, echocardiography could not be performed on all patients, and the diagnosis of myocarditis could not be confirmed by cardiac biopsy or cardiac MRI in any patient.

Conclusion

The prolongation of QRS duration was as significant as other inflammatory parameters and a possible independent risk factor to predict mortality due to COVID-19. ECG at the first admission of patients may provide insight into the prognosis of COVID-19. Compared to other examinations, easier and faster results obtained by ECG will be beneficial in this respect.

Scientific Responsibility Statement

The authors declare that they are responsible for the article's scientific content including study design, data collection, analysis and interpretation, writing, some of the main line, or all of the preparation and scientific review of the contents and approval of the final version of the article.

Animal and human rights statement

All procedures performed in this study were in accordance with the ethical standards of the institutional and/or national research committee and with the 1964 Helsinki declaration and its later amendments or comparable ethical standards. No animal or human studies were carried out by the authors for this article.

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Conflict of interest

None of the authors received any type of financial support that could be considered potential conflict of interest regarding the manuscript or its submission.

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